A Molecular Dialogue Between the Brain and Face

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Clinicians have long recognized that a relationship exists between the development of the forebrain and the face. Forebrain defects are frequently associated with distinctive facial features [1], allowing experienced clinicians to diagnose brain anomalies based on a patient's facial appearance. Traditionally the forebrain has been viewed as a scaffold upon which the face develops, and this observation has led to the notion that forebrain defects are accompanied by facial defects due primarily to mechanical influences of one tissue on the other [2].

While the brain plays a substantial physical role in shaping the face, the forebrain and face are also intimately linked because morphogenesis of both structures requires tissue interactions among forebrain neuroepithelium, neural crest, and ectoderm of the face [3]. All of the facial primordia are populated by mesenchymal cells derived principally from the neural crest and are surrounded by epithelia of ectodermal and in some cases, endodermal origin. Through a series of poorly understood molecular and cellular events, these undifferentiated buds of tissue are transformed into the anatomically intricate forehead, nose, cheeks, lips, jaws, and chin. How do cells within the developing facial primordia acquire the spatial information necessary to produce such highly integrated morphological components? We propose that regions of neural and facial epithelia act as organizing centers, which mediate dorsoventral, mediolateral, and proximodistal patterning of the FNP through the regulation of bone morphogenetic proteins (Bmps). We will provide data demonstrating that frontonasal process (FNP) ectodermal cues specify dorsoventral patterning in the mid- and upper face. We will also show data indicating that the neuroepithelial domain of Sonic hedgehog (Shh; 4) establishes the mediolateral axis of the FNP, in part by mediating migration of FNP neural crest to the facial midline. Collectively, these data offer insight into the mechansims by which epithelial-mesenchymal interactions govern development of the mid- and upper-face, and provide a fundamental framework upon which preventive, diagnostic, and therapeutic approaches to treating birth defects can be developed.

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